REMARKS

I. Claim status

Claims 1-16 are pending in the application. Claims 1, 4-6, 10-12, 14 and 15 have been amended. Claims 2, 3, and 6-16 have been withdrawn by the Examiner.

The claim amendments are either deletions of non-elected subject matter (subject to the request for traverse below), changes of form or modifications that set forth or identify antecedent basis. Thus, the amendments are supported throughout the specification and by the original claims as filed. No new matter has been added.

II. Priority and Requirement for Information

The Office has issued a Requirement for Information under 37 CFR 1.105 ("the Requirement") and noted that "the foreign priority papers filed in the present application cannot be relied upon because a translation of said papers has not been made of record." Office Action at page 2. Specifically, the Office required information regarding the abstract of Isomura et al., presented at the 53rd Annual Meeting of the American Society of Human Genetics on November 6, 2003, to determine whether written copies of the presentation constitutes prior art. See the Requirement.

Applicants submit herewith a certified English translation of the foreign priority application, Japanese Application No. 2003-375369, filed November 5, 2003, to perfect the foreign priority claim. Because the foreign priority application was filed before the presentation of Isomura et al., the English translation of the foreign priority application removes Isomura et al. as prior art and renders the Requirement unnecessary. Therefore, there is no need to provide the information requested in the Requirement.

III. Election/Restrictions

The Office has withdrawn claims 2-3 and 6-16 from further consideration as allegedly being drawn to a "nonelected invention and non-elected species." Office Action at pages 3-4. Applicants respectfully traverse.

In the Response to Restriction Requirement filed on October, 2009, Applicants elected, with traverse, to prosecute Group I, claims 1-9, allegedly drawn to methods for predicting risk of granulocytopenia. Applicants also elected to prosecute the following species: a genetic polymorphism at the 11th nucleotide of the sequence defined by SEQ ID NO: 6 in BUB1b gene.

As amended, claim 1 only recites genetic polymorphisms in the BUB1b gene, including the elected species "a genetic polymorphism at the 11th nucleotide of the sequence defined by SEQ ID NO: 6 in BUB1b gene." Claim 6, as amended, depends from claim 1. Claim 7-9 all ultimately depend from claim 6. Since claim 1 falls within the scope of the elected invention and recites the elected species, Applicants respectfully request that claims 6-9 be reinstated for further prosecution.

IV. Oath/Declaration

The Office states that the oath or declaration is defective because it does not identify the citizenship of each inventor. Office Action at page 4.

Applicants submit herewith a Supplemental Declaration and Power of Attorney identifying the citizenship of each inventor.

V. Specification

The Office has objected to the specification for containing an embedded hyperlink and/or other form of browser-executable code. Office Action at page 4.

The specification has been amended to delete the embedded hyperlink. Applicants respectfully request withdrawal of the objection.

V. Rejection under 35 U.S.C. § 112, second paragraph

The Office has rejected claims 1 and 4-5 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as invention. Office Action at page 5.

Specifically, claim 1 has been rejected for allegedly being incomplete for omitting essential steps. Id. The Office contends that "the only method step of the claim requires identifying one or more polymorphisms; there is no indication as to how (or even whether) this relates to predicting risk." Id. As amended, claim 1 now recites the additional step of "assessing a genotype(s) of said one or more genetic polymorphisms to thereby predict the risk of the occurrence of granulocytopenia caused by paclitaxel therapy in said subject."

Regarding claims 4-5, the Office contends that "it is not clear how a 'gene' may actually be a 'genotype'; thus the meaning of this claim language is unclear," and required clarification. Claim 4 has now been amended to recite:

> ...wherein the risk of the occurrence of granulocytopenia is predicted to be high in the case where the gene isolated from the subject [[is]] <u>exhibits</u> one or more of the following (A) through (E):
>
> (A) the genotype at the 11th nucleotide of the sequence defined by SEQ ID NO: 6 in BUB1b gene is A/A;...

Claim 5 has also been similarly amended.

Consequently, Applicants request the rejection of claims 1 and 4-5 under 35 U.S.C. § 112, second paragraph, be withdrawn.

VI. Rejection under 35 U.S.C. § 112, first paragraph

The Office has also rejected claims 1 and 4-5 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Office Action at page 6. In particular, the Office contends that "no true association between the elected polymorphism and granulocytopenia risk has as yet been established," and "it would clearly require undue experimentation to use applicants' claimed invention." See Office Action at page 10. To support those contentions, the Office alleges that the sample size of the patients studied in the Examples of the specification, namely 54 breast cancer patients, is "extremely small." Office Action at page 8. Thus, the Office concludes that an ordinary artisan would recognize that that "applicants' findings have yet to be replicated." Id. The Office further cites Ioannidis et al. (The Lancet 361:567-571 [Feb. 2003]) ("Ioannidis"), and Dahlman et al. (Nature Genetics 30: 149-150 [Feb. 2002]) ("Dahlman") to support the contention of "high degree of unpredictability" in the art of genetic associations.

Applicants respectfully disagree. As is well established, the enablement requirement refers to the requirement of 35 U.S.C. § 112, first paragraph, that the specification describe *how to make and how to use the invention*. MPEP 2164. Applicants draw the Office's attention to the following instructions in the specification regarding how to identify genetic polymorphisms and how to predict the risk of the

occurrence of granulocytopenia caused by paclitaxel therapy, based on the genetic association that is disclosed in the specification:

> In the method of the present invention, peripheral blood, other body fluid, cells or tissue and so forth is collected from subjects scheduled to be treated with paclitaxel or are currently being administered paclitaxel, then genomic DNA is prepared from these samples in accordance with established methods. When necessary, a sequence at a site to be typed is amplified. Typing of genetic polymorphisms can be easily carried out using various methods known or being developed in the art. Examples of typing methods include, but are not limited to, the direct sequencing method, invader method, TaqMan method, MALDI-TOF/MS method, primer extension method and hybridization method.
>
> . . .
>
> According to the method of the present invention, the risk of the occurrence of adverse side effects caused by paclitaxel therapy can be predicted by typing one or more SNP sites identified in the present invention and referring to statistical data indicated in the examples to be described later.

See the specification at page 22, second paragraph, and at page 24, third paragraph. Thus, Applicants respectfully submit that the instant specification provides more than sufficient disclosure regarding how to use the invention for the claimed method, which goes to the core of enablement.

As such, it appears, while not expressly stated, that the Office bases the enablement rejection on lack of credible utility, as the Office contends that "applicants' findings have yet to be replicated and were obtained using an extremely small sample of patients," and cited two references in support of that statement. Office Action at 7-9. However, the MPEP, citing Federal Circuit case law, provides the following guidance:

> ***Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development***. The

> stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). . .
>
> These general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. If the asserted utility is credible, there is no basis to challenge such a claim on the basis that it lacks utility under 35 U.S.C. 101.

See MPEP 2107.01 III. (emphasis added). While the cases and the MPEP section address therapeutic agents and processes for treating diseases, Applicants submit that the same general principles apply to diagnostic methods, and for all three types of inventions, there is no requirement to prove the claimed invention to a clinical certainty.

Regardless, the clinical data in this invention is impressive. Based on the data obtained from 54 breast cancer patients, the present application discloses statistically significant, strong correlations between CYP2C8/BUB1b genes and granulocytopenia. For instance, the study described in the Example section demonstrated small p values ($p < 0.02$), which are used to measure statistical significance (probability), and high odds ratios, which are used to measure the strength of the genetic association (odds ratios > 3, some as high as 10). *See* the specification at page 31, Tables 12-13. Thus, Applicants respectfully submit that the finding is based on such statistical significance and strong correlations that the credible utility is not lacking.

The Office cites references Ioannidis and Dahlman to support the contention of "high degree of unpredictability" in the art of genetic associations. However, the "large studies" described in those references exhibited much higher p values and/or much

lower odds ratios than the study in the present disclosure. See Table 12-13 of present specification (showing $p < 0.02$; odds ratio > 3); Ioannidis at page 569, last three columns of the table (showing that less than 50% of the studies have $p < 0.1$, thus judged to be statistically significant, but all of those studies have low odds ratios less than 2); and Dahlman at page 149, Table 1, last column (showing $p > 0.09$). Those distinctions indicate that, even though the patient population studied in the present disclosure was much smaller than those of the large studies, the sample size was sufficient to demonstrate statistically more significant and stronger genetic associations than the large studies described in the references.

Furthermore, those large studies described in the two cited references attempted to detect genetic associations for complex diseases such as diabetes, heart diseases, Central Nervous System (CNS) diseases, and cancer. As those in the art recognize, a myriad of risk factors, genetic and non-genetic or environmental, could contribute to those diseases, which increases the difficulty of detecting true genetic associations. In contrast, the claimed invention concerns granulocytopenia caused by paclitaxel therapy.

Because of the foregoing distinctions, Applicants respectfully submit that the cited references simply cannot undermine the credibility of the claimed invention.

The Office also states that the entry of the SNPs (rs2277559 and ss3214454) in the dbSNP database discloses the existence of the elected polymorphism but is silent regarding any risk associations. Office Action at page 9. Therefore the Office concludes that "the prior art cannot be relied upon in the present case with regard to enablement of methods for 'predicting the risk of the occurrence of granulocytopenia caused by paclitaxel therapy.'" Id. For all the reasons discussed above, the claimed invention clearly satisfies the enablement requirement. The lack of teaching of any risk

associations in the cited prior art only supports the novelty and non-obviousness of the claimed invention. Those database entries do not in any way undermine the utility of the claimed invention

Therefore, Applicant respectfully request withdrawal of this rejection.

VII. Rejection under 35 U.S.C. § 102

The Office has further rejected claim 1 under 35 U.S.C. 102(b), as allegedly being anticipated by the dbSNP entry for rs2277559, particularly, the portion of that entry set forth in ss3214454 (Database of Single Nucleotide Polymorphisms (dbSNP). Bethesda (MD): National Center for Biotechnology Information, National Library of Medicine. dbSNP accession: rs2277559 and ss3214454 (Build 100, publicly available 24 Oct 2001. Available from: http://www.ncbi.nlm.nih.qov/SNP/). Office Action at pages 10-11. Specifically, the Office contends that "claim 1 as written does not appear to require any step(s) requiring or resulting in prediction of granulocytopenia risk; rather, the only actual method step set forth in the claim merely requires 'identifying in a gene isolated from' a subject the elected polymorphism 'at the 11th nucleotide of the sequence defined by SEQ ID NO: 6 in BUB1b.'" Office Action at page 11. Hence, the Examiner concludes that the dbSNP entry for ss3214454 anticipates the claimed invention. Applicants respectfully traverse.

Simply to clarify, as set forth above, claim 1 now recites "assessing a genotype(s) of said one or more genetic polymorphisms to thereby predict the risk of the occurrence of granulocytopenia caused by paclitaxel therapy in said subject." It is well established that anticipation requires that a single reference provide each and every recited element. M.P.E.P. 2131. As the Office has admitted, "the dbSNP entry for

rs2277559, particularly, the portion of that entry set forth in ss3214454. . .discloses the existence of the elected polymorphism but is silent regarding any risk associations." Office Action at page 9. Nothing in the dbSNP entry teaches "assessing a genotype(s) of said one or more genetic polymorphisms to thereby predict the risk of the occurrence of granulocytopenia caused by paclitaxel therapy in said subject." Thus, regardless of any other distinctions between the dbSNP entry and the invention of claim 1, this difference is sufficient to avoid anticipation. Therefore, Applicants respectfully request withdrawal of this rejection.

VIII. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: June 17, 2010

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